IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2012; 9(1):68-73

Research Paper

Clinicopathological Characteristics and Prognosis of Non-Small Cell Lung Cancer Patients Associated with a Family History of Lung Cancer

Shuji Haraguchi[1, 2]✉, Kiyoshi Koizumi[1, 2], Iwao Mikami[1, 2], Okamoto Junichi[1, 2], Yoshihito Iijima[1, 2], Takayuki Ibi[1, 2], Kazuo Shimizu[2]

1. Department of Surgery, Division of Thoracic Surgery, Nippon Medical School, Tokyo, Japan.
2. Department of Biological Regulation and Regenerative Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan.

✉ Corresponding author: Shuji Haraguchi, MD, Department of Surgery, Division of Thoracic Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan. Tel., 03-3822-2131 (business), 048-261-9733 (home), Fax, 03-5685-0985 (business), E-mail, shuji@nms.ac.jp

Received: 2011.10.04; Accepted: 2011.11.20; Published: 2011.11.30

Abstract

Introduction: Clinicopathological characteristics and prognosis of non-small cell lung cancer (NSCLC) patients with a family history of lung cancer (FHLC) have not been well established.

Methods: Clinical records of patients with NSCLC treated at our institute from 1982 to 2010 were reviewed with special reference to family history of lung cancer and clinico-pathological factors including patient's outcome. Univariate analyses of the factors between the groups of FHLC and non-FHLC were performed using unpaired two-tailed t tests or the chi-square test. The Cox proportional hazards model was used to evaluate the hazard ratio of death.

Results: Of the 1013 NSCLC patients, 124 (12.2%) had a FHLC of whom 119 (96%) were the first-degree relatives. The frequency of early stages of lung cancer was high in both groups of FHLC and non-FHLC patients. Patients with FHLC had a significantly higher frequency of early pathological stages and a prepomderance of adenocarcinoma, and a hazard ratio of death of 0.870 (95% confidence interval: 0.599-1.263, p value: 0.465) compared with the non-FHLC patients.

Conclusions: NSCLC patients with FHLC could be characterized by early pathological stages and preponderance of adenocarcinoma, however they were not at a decreased hazard ratio of death. These findings emphasize the importance of early detection of lung cancer and em-ployment of less invasive therapeutic interventions.

Key words: non-small cell lung cancer, family history of lung cancer, clinicopathological characteristics, prognosis, hazard ratio of death.

Introduction

A familial aggregation of lung cancer is reported in various populations even in patients without a hereditary cancer syndrome [1-7]. However, the clinical characteristics and prognosis of lung cancer patients associated with a family history of lung cancer (FHLC) have not been well established [6, 7]. Several studies have examined the relationship between FHLC and lung cancer risk and have reported a favorable correlation [1, 2, 6, 7, 8-13], whereas others have not observed such an association [14, 15]. To

provide further insights into this issue, we conducted a comprehensive review of the clinical records of all patients with non-small cell lung cancer (NSCLC) treated at our institute during a long period of 28 years. Subsequently, we assessed the clinicopathological characteristics and prognosis of patients with FHLC and compared the results with lung cancer patients without FHLC (non-FHLC).

Methods

Subjects

From February 1982 to March 2010, 1,502 patients underwent a resection for NSCLC at the Division of Thoracic Surgery, Department of Surgery of Nippon Medical School. Of these, 387 patients were excluded from the study due to the lack of a detailed family history. Therefore, 1,013 patients including 723 men and 290 women were analyzed in the present study. Of the 1,013 patients, 125 (12.2%) including 87 men and 38 women were patients with FHLC (FHLC group).The mean age of the patients with FHLC and non-FHLC groups were 66 years old (range, 38-84 years old) and 65 years old (range, 20-95 years old), respectively. The FHLC group had 732 first-degree relatives, and 120 patients had 130 first-degree relatives with lung cancer including 89 men and 41 women (65 siblings, 39 fathers, 25 mothers, and 1 child) and 6 patients had 6 second-degree relatives with lung cancer including 5 men and 1 women (3 uncles, 1 aunt, 1 grandfather, and 1 nephew). The lung cancers of all the patients were staged clinically and pathologically according to the seventh edition of TNM staging system for lung cancer [16]. In this series, parents, siblings and offspring are considered as first-degree relatives, grandparents, uncles, aunts, and nephews are second-degree relatives, and cousins as third-degree relatives [2, 3, 6, and 7].

The postoperative pulmonary functions were predicted according to a simplified system, which we developed using plain chest roentgenograms of patients with primary lung cancer [16, 17]. The ppoFEV1.0 is (42-R)/(42-T) × preoperative FEV1.0, where R is the number of subsegments scheduled for lung resection and T is number of tumor-related subsegments. T is determined as follows: (a) if a tumor is located in the periphery of the lung, the T factor is equal to 1 in the case of a tumor 3 cm or less in its largest dimension and equal to 2 in the case of a tumor more than 3 cm in its largest dimension; and (b) if a tumor obstructs large airways, the T factor is equal to the number of subsegments involved in atelectasis or postobstructive pneumonia [17, 18].

Statistics

Statistical analyses were performed between the FHLC and non-FHLC groups, using IBM SPSS Statistics version 19 (IBM SPSS, New York, USA). Only first-degree relatives were used in the analyses because we suspected incomplete information of second-degree relatives from disproportion between numbers of first- and second-degree relatives. Univariate analyses between the groups were performed by means of unpaired two-tailed t tests or the chi-square test, using age, sex, smokers versus never smokers, symptoms at the time of discovery of lung cancer (asymptomatic versus symptomatic), with and without diagnosis before surgery, operative procedures (pneumonectomy versus others), pathological stage (stage I or II versus stage III or IV), histological type of lung cancer (adenocarcinoma versus others).

For statistical analyses of prognostic factors for the overall survival of lung cancer patients, we partitioned the patients by age (above versus below the median of 65 years), sex, smokers or never smokers, the FHLC group versus the non-FHLC group, symptoms at diagnosis (asymptomatic versus symptomatic), with and without diagnosis of lung cancer before surgery, operative procedures (pneumonectomy versus others), pathological stage (stage I or II versus stage III or IV), and histological type of lung cancer (adenocarcinoma versus others). For the univariate analyses, the overall survival for subgroups described above was statistically analyzed using Kaplan-Meier estimated survival curves, and the significance of the difference was analyzed by the log-rank test. After adjusting for those prognostic factors, the Cox proportional hazards model was used to evaluate the risk of death of the FHLC group compared with the non-FHLC group. A $p<0.05$ was considered significant.

Results

Site of malignancy in the first- and second-degree relatives are shown in Table 1. Lung was the secondly frequent site (17.9%). Of 125 patients with FHLC, 85 patients (68%) had adenocarcinoma, 32 (25.6%) had squamous cell carcinoma, 5 (4%) had large cell carcinoma, and 3 (2.5%) had others. Of 125 patients with FHLC, 115 patients (92%) had 1 relative with lung cancer, 9 (7.2%) had 2 relatives with lung cancer, and 1 (0.8%) had 3 relatives with lung cancer. Of 732 first-degree relatives, 10 patients had other smoking-related cancers (laryngeal, esophageal, pancreas, bladder carcinoma each in 2, maxillary and kidney carcinoma each in 1).

Table 1. Site of cancer in the family of lung cancer patients.

Location	Number (%)
1 Stomach	261 (34.3)
2 Lung	136 (17.9)
3 Colon (including rectum)	80 (10.5)
4 Liver	52 (6.8)
5 Uterus	41 (5.4)
6 Mammary gland	28 (3.7)
7 Esophagus	26 (3.4)
8 Pancreas	21 (2.8)
9 Larynx	15 (2.0)
10 Prostate	14 (1.8)
11 Bladder	11 (1.4)
12 Central nerve system	11 (1.4)
13 Blood	9 (1.2)
14 Skin	8 (1.1)
15 Lymph node	8 (1.1)
16 Kidney	7 (0.9)
17 Gall bladder and bile duct	6 (0.8)
18 Tongue	5 (0.7)
19 Bone	5 (0.7)
20 Ovary	4 (0.5)
21 Maxillary antrum	4 (0.5)
22 Pharynx	2 (0.3)
23 Thyroid	2 (0.3)
24 Oral	1 (0.1)
25 Gingival	1 (0.1)
26 Urinary tract	1 (0.1)
27 Peripheral nerve	1 (0.1)

The clinicopathological characteristics of the FHLC and non-FHLC groups are shown in Table 2. The FHLC group had significantly early pathological stages of lung cancer as compared with the non-FHLC group. The FHLC group had a significantly more frequency of adenocarcinoma as compared with the non-FHLC group. The clinicopathological characteristics of the FHLC and non-FHLC groups in adenocarcinoma patients alone are shown in Table 3. There was no significant difference in frequency of early pathological stages of lung cancer between the FHLC and non-FHLC groups.

Univariate analyses of the prognostic factors for the overall survival of lung cancer patients revealed that sex, symptoms at diagnosis, pathological stage, operative procedure, never smokers, and histology were the significant risk factors (Table 4). After adjusting these risk factors, the FHLC group had a hazard ratio of death of 0.820 (95% confidence interval: 0.558-1.204, p value: 0.311) as compared with the non-FHLC group (Table 5).

The 5-year overall survival was 65% for the FHLC group and 58% for the non-FHLC group (p=0.1399). The 5-year overall survival for lung cancer patients with p-stage I /II was 71.2% in the FHLC group and 70.7% in the non-FHLC group (p=0.8834). The 5-year overall survival for lung cancer patients with p-stage I /II and adjuvant therapy was 69 .2% in the FHLC group and 68.1% in the non-FHLC group (p=0.981). The 5-year overall survival for lung cancer patients with p-stage III/ IV was 36.2% in the FHLC group and 29.4% in the non-FHLC group (p=0.4986). The 5-year overall survival for lung cancer patients with p-stage III/ IV and adjuvant therapy was 35.4% in the FHLC group and 49.5% in non-FHLC group (p=0.195).

Table 2. Clinicopathological characteristics of patients with family history of lung cancer (FHLC) versus without family history of lung cancer (non-FHLC).

	FHLC (%)	*non-FHLC (%)*	*P value*
Number of patients	120	889	NAs
Age	66±9	65±10	0.446
<50 years	5 (4)	60 (7)	0.288
Sex			
Male	84 (71)	637 (72)	
Female	35 (29)	252 (28)	0.809
Smokers	90 (76)	666 (75)	
Never smokers	29 (24)	223 (25)	0.866
ppoFEV1.0 (L)	1.8±0.5	1.7±0.5	0.052
Asymptomatic	76 (64)	598 (67)	
Symptomatic	43 (36)	291 (33)	0.459
Diagnosis before surgery	102 (86)	774 (87)	0.682
Operative procedures			
Pneumonectomy	8 (7)	89 (10)	
Others	111 (93)	800 (90)	0.253
Adjuvant therapy	56 (47)	410 (46)	0.847
Pathological stage of lung cancer			
I, II	92 (77)	605 (68)	
III, IV	27 (23)	284 (32)	0.040*
Histological type of lung cancer excluding MPLC			
Adenocarcinoma	79 (66)	490 (55)	
Others	40 (32)	399 (45)	0.020*

NA, not applicable; MPLC, multiple primary lung cancer; *, statistically significant.

Table 3. Clinicopathological characteristics of adenocarcinoma patients with family history of lung cancer (FHLC) versus without family history of lung cancer (non-FHLC).

	FHLC (%)	*non- FHLC (%)*	*P value*
Number of patients	79	490	NAs
Age	65 ± 9	65 ± 10	0.366
<50 years	4 (5)	34 (7)	0.535
Sex			
Male	50 (63)	294 (60)	
Female	29 (37)	196 (40)	0.579
Smokers	54 (68)	303(62)	
Never smokers	25 (32)	187 (38)	0.266
ppoFEV1.0 (L)	1.8±0.5	1.8±0.6	0.912
Asymptomatic	60 (76)	372 (76)	
Symptomatic	19 (24)	118 (24)	0.995
Diagnosis before surgery	67 (85)	415 (85)	0.979
Operative procedures			
Pneumonectomy	4 (5)	23 (5)	
Others	75 (95)	467 (95)	0.886
Adjuvant therapy	39 (49)	227 (46)	0.615
Pathological stage of lung cancer			
I, II	60 (76)	352 (72)	
III, IV	19 (24)	138 (28)	0.448

NA, not applicable; MPLC, multiple primary lung cancer.

Table 4. Univariate analyses of the prognostic factors for the overall survival of lung cancer patients.

Groups		Overall survival rates (%)					P value (Log-rank)
		Years					
		1	2	3	4	5	
Age <65 years	(n=459)	84	74	67	63	61	
Age ≧65 years	(n=549)	85	75	67	62	57	0.410
Sex Male	(n=721)	82	72	63	57	53	
Sex Female	(n=281)	91	82	77	75	73	0.000*
Never smokers	(n=252)	93	82	75	72	70	
Smokers	(n=756)	81	72	65	59	55	0.000*
Non-FHLC	(n=889)	84	74	67	61	58	
FHLC	(n=119)	88	81	71	69	66	0.098
Asymptomatic	(n=674)	91	84	78	72	69	
Symptomatic	(n=334)	70	56	46	42	39	0.000*
Preoperative LC diagnosis	(n=876)	84	74	66	61	58	
Postoperative LC diagnosis	(n=132)	86	79	73	71	64	0.229
Pneumonectomy	(n=97)	52	44	38	34	31	
Others	(n=911)	88	78	70	65	62	0.000*
Pathological stage I, II	(n=697)	92	86	80	75	71	
III, IV	(n=311)	65	48	37	31	30	0.000*
Adenocarcinoma	(n=569)	89	81	74	68	64	
Others	(n=439)	78	66	59	55	52	0.000*

FHLC, family history of lung cancer; LC, lung cancer; *, statistically significant.

Table 5. Multivariate Cox proportional hazards regression analysis.

Factors	Hazard ratio of death	95%CI	p value
Pathological stage (III-IV vs. I-II)	3.432	2.723-4.325	0.000*
Symptoms (Present vs. absent)	2.090	1.657-2.636	0.000*
Sex (Female vs. male)	0.666	0.478-0.927	0.016*
Procedures (Pneumonectomy vs. others)	1.237	0.907-1.688	0.179
Pathology (Adenocarcinoma vs. others)	0.883	0.697-1.120	0.306
FHLC (Present vs. absent)	0.820	0.588-1.204	0.311
Smoking history (Smokers vs. never smokers)	1.118	0.794-1.574	0.522

*, Statistically significant.

Discussion

Clinicopathological characteristics and prognosis of NSCLC patients with FHLC have not been well established in the literature [6, 7]. The present study showed that 78% of the FHLC group and 68% of the non-FHLC group were diagnosed at pathological stage I and II as compared with 18% and 15% respectively in the series reported by of Ganti et al [6] and 38% and 42% respectively in the series reported by of Lin et al [7]. The high frequency of early stages in the FHLC and non-FHLC groups may be attributable to the universal healthcare practice in Japan. For example, patients aged 40 years or over can have the annual chest X-ray program in Tokyo. Of 80 asymptomatic patients, 73 patients were from the screening programs.

In addition, the lung cancers in FHLC group were detected significantly at early stages as compared with the non-FHLC group. It is suggested that the knowledge of FHLC allows the patient to recognize their predisposition to lung cancer and thus regularly attempt hospital visit for check-up.

The present series had a high percentage of never-smoker (24% of the FHLC group and 32% of adenocarcinoma patients). The percentage of never smoker in the Eastern countries seems to be higher than that in the Western countries. In German, 4.1% and 5.3% of the patients aged below 45 years and between 55-69 years in the FHLC group were never-smoker [13]. In the United States, 5% of the FHLC group was never-smoker compared to 36% in China [6]. Furthermore, 33% of the FHLC group was never-smoker in the other series in Japan [12].

Squamous cell carcinoma has been reported to be mostly associated with familial clustering of cancer, paticularly among women, persons younger than 57 years, and individuals who smoked for fewer than 20 years [4]. Recently, patients in the FHLC group, compared to those in the non-FHLC group were diagnosed at earlier ages and presented more cases of adenocarcinomas in China [7]. In our series a preponderance of adenocarcinoma were observed, but patients in the FHLC group were not diagnosed at earlier ages, even in adenocarcinoma patients. Therefore, further study is necessary to clarify whether the difference in epidemiological findings is district-related or is due to the race.

The multivariate analysis of the prognostic factors showed that pathological stages, symptoms at the time of discovery of lung cancer, and gender were risk factors in the present series. Male patients significantly died of lung cancer, other disease, and operative cause than female patients. Male patients had significantly more advanced pathological stages than female patients. In addition, male patients had significantly higher operative mortality due to severe comorbidity (data not shown).

An adjusted hazard ratio of death of 1.65 in the FHLC group compared with the non-FHLC group was found in the series reported by Ganti et al in the United States [6]. This risk was especially increased in those with an affected first-degree relative. This series had high frequency of small cell lung cancer. On the contrary, a significantly better prognosis was found in the FHLC group than the non-FHLC group in the series reported from China [7]. They also reported poorer response rate to chemotherapy in the FHLC group with advanced stages. However, in our study, there was no significant difference in an adjusted hazard ratio of death between the FHLC and non-FHLC groups. In support of this finding, a recent study on a large cohort of women with lung cancer in China also showed that lung cancer risk was not increased among women with a family history of lung cancer [15]. We found that adjuvant therapy in the early and advanced stages does not affect the survival in the FHLC and non-FHLC groups. Further, early detection of lung cancer in the FHLC group contributed to an improved survival, but didn't reach a significant level

Conclusions

NSCLC patients with FHLC demonstrate an early pathological stage and a preponderance of adenocarcinoma, but are not at a decreased hazard ratio of death as compared with those without FHLC. These findings emphasize the importance of early detection of lung cancer and employment of less invasive therapeutic intervention.

Authorship

SH was the principal investigator of the study and drafted the manuscript. KK and IM participated in the design of the study and the statistical analyses. OJ contributed in the design of the study. YI and TI participated in the data collection and analyses. KS supervised the project and helped draft the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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